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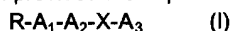
(54) **Peptides inhibiting interleukin 1- β release useful as antiinflammatory agents.**

(57) Compounds of formula $R-A_1-A_2-X-A_3$ wherein R is H, a protecting group or optionally substituted benzyloxy, A_1 is an α -hydroxy or α -amino acid residue or a radical (α) as defined hereinafter, A_2 is an α -hydroxy or α -amino acid residue or A_1 and A_2 form together a pseudo-dipeptide or a dipeptide mimetics residue or a radical (aa), (bb) or (cc) as defined hereinafter, X is a residue derived from Asp wherein A_3 is $-CH_2-X_1-CO-Y_1$, $-CH_2-O-Y_2$, $-CH_2-S-Y_3$ or $-CH_2-(CO)_m-Y_6$ wherein X_1 is O or S, m is 0 or 1 and Y_1 , Y_2 , Y_3 and Y_6 are as defined herein after, have pharmacological activity, e.g. IL-1 β release inhibiting properties.

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The present invention relates to peptides having pharmaceutical utility, processes for their production, pharmaceutical compositions comprising them and their use as pharmaceuticals.

More particularly the present invention provides a compound of formula I



wherein

R is hydrogen, an amino or hydroxy protecting group or optionally ring substituted benzyloxy,

A₁ is an α-hydroxy acid residue; an amino acid residue or a thiocarbonyl analogue thereof having each an optionally protected side chain; or a radical of formula (α)

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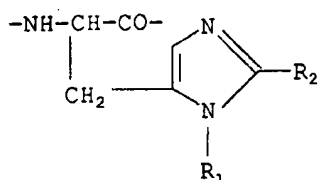


wherein ring A is optionally substituted by hydroxy or C₁₋₄alkoxy and R_a is CO or CS

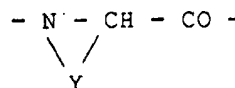
and either

i) A₂ is an α-hydroxy acid residue, -NH-CHR₃-CO-

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or



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wherein

R₁ is C₁₋₄alkyl

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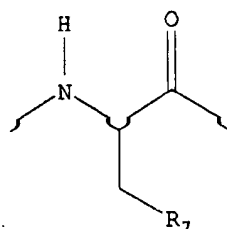
R₂ is H, halogen, C₁₋₄alkyl, CF₃ or trityl,

R₃ is an optionally protected side chain residue of an α-amino acid, and

Y is C₂₋₆alkylene optionally substituted by OH, CH₃, C₂H₅, oxo, ketal or halogen,

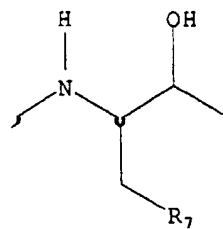
X is a radical of formula (a) or (b)

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(a)



(b)

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wherein R₇ is -CO₂H, -CONHOH or a bioisosteric group,

A₃ is -CH₂-X₁-CO-Y₁; -CH₂-O-Y₂; or -CH₂-S-Y₃; wherein X₁ is O or S, Y₁ is a cycloaliphatic residue; optionally substituted aryl; optionally ring substituted diphenylmethyl; piperidino; or optionally substituted mono-, bi- or tricyclic heteroaryl; Y₂ is a cycloaliphatic residue; optionally ring substituted diphenylmethyl; or optionally substituted bi- or tricyclic heteroaryl; Y₂ being also optionally substituted pyridyl or aryl when A₁ is other than an α-hydroxy acid residue and A₂ is other than -NH-CHR₃-CO-; and Y₃ is a cycloaliphatic residue; tri-(C₁₋₄alkyl)methylcarbonyl, di-(C₁₋₄alkyl)aminothiocarbonyl, 4-nitro-phenyl, 2,6-dichloro-benzoyl; 2,3,6-trichloro-4-pyridyl, a 5-membered nitrogen-containing heterocyclic radical or optionally substituted bi- or tricyclic heteroaryl; Y₃ being also optionally substituted pyridyl or aryl when A₁ is other than an α-hydroxy acid residue and A₂ is other than -NH-CHR₃-CO-;

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or

ii) A₂ is a radical of formula (c)

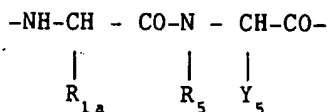


wherein

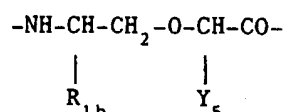
R_4 is H or C_{1-4} alkyl

R_6 is CO or CS

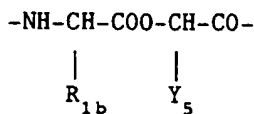
Y_4 is $-(CH_2)_s-N(C_{1-4}alkyl)_2$ or optionally protected $-(CH_2)_s-NH-cyclohexyl$ wherein s is 1, 2, 3 or 4; or A_1 and A_2 form together a radical of formula (aa), (bb) or (cc)



(aa)

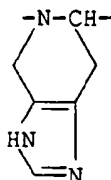


(bb)



(cc)

wherein R_{1a} and R_5 form together C_{2-6} alkylene or C_{2-6} alkenylene and Y_5 is an optionally protected side chain residue of an α -amino acid; or Y_5 has one of the significances given above for Y_4 , or R_5 and Y_5 form together



or R_5 is 2,3-dihydro-2-indanyl, Y_5 is H and R_{1a} has independently one of the significance given for R_{1b} , and R_{1b} is an optionally protected side chain of the amino acid residue or thiocarbonyl analogue A_1 indicated above,

or A_1 and A_2 form together a pseudo-dipeptide or a dipeptide mimetics residue,

X is a radical of formula (a) or (b) as defined above, and

A_3 is $-CH_2-X_1-(CO)_m-Y_6$ wherein X_1 is as defined above, m is 0 or 1 and Y_6 is a cycloaliphatic residue; tri- $(C_{1-4}alkyl)methyl$; optionally ring substituted diphenylmethyl; optionally substituted aryl; or an optionally substituted mono-, di- or tricyclic heteroaryl residue

with the provisos that

i) Y_1 in A_3 is other than optionally substituted aryl or pyridyl when A_1 is other than an α -hydroxy acid residue, A_2 is $-NH-CHR_3-CO-$ and R_7 in (a) or (b) is optionally esterified COOH,

ii) Y_5 in (aa) is in R configuration when it is the residue of an optionally protected side chain residue of an α -amino acid, Y_6 is optionally substituted aryl and R_7 is optionally esterified COOH,

and the physiologically-hydrolysable and -acceptable esters or amides thereof when R_7 is $-CO_2H$, in free form, in salt form or in the form of complexes.

By amino acid is meant a naturally occurring or commercially available or non natural amino acid or an optical isomer thereof. A non natural amino acid is an amino acid which is not incorporated into a protein under mRNA direction, e.g. β -Nal, a fluoro- α -amino acid such as fluoroalanine, cyclohexylalanine, trimethylsilyl-Ala,

benzimidazol-2-yl-methyl, 1H-1,2,4-triazol-3-yl-methyl, pyrazol-3-yl-methyl or indazol-3-yl-methyl.

Examples of protecting groups as R are e.g. disclosed in "Protective Groups in Organic Synthesis", T. W. Greene, J. Wiley & Sons NY (1981), 219-287, for example acyl such as formyl, acetyl, methoxysuccinyl, hydroxysuccinyl, benzoyl or phenylacetyl, each of the two latter being optionally substituted on the phenyl ring with e.g. p-methoxycarbonyl, p-methoxy or p-nitro; trityl; alkoxycarbonyl such as methoxycarbonyl, t-butyloxycarbonyl or i-butyloxycarbonyl; allyloxycarbonyl; arylmethoxycarbonyl such as 9-fluorenylmethoxycarbonyl or benzyloxycarbonyl optionally substituted on the phenyl ring with p-methoxy, p-nitro, p-chloro or m-phenyl; aralkyl such as benzyl or phenethyl optionally ring substituted with p-methoxy, p-nitro or p-chloro, or naphthylmethyl; aralkoyl such as phenacetyl, phenylpropionyl or naphthoyl; arylsulfonyl or aralkylsulfonyl such as phenylsulfonyl or benzylsulfonyl each being optionally ring substituted with p-methyl or p-methoxy, or naphthylsulfonyl optionally ring substituted with e.g. amino or di(C₁₋₄alkyl)amino.

Examples of hydroxy protecting groups as R are e.g. as disclosed hereinafter for aliphatic or aromatic hydroxy functionalities.

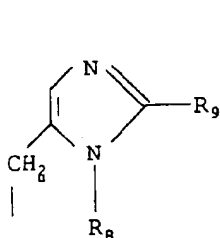
When the side chain of the natural or unnatural amino acids includes heteroatoms such as O, S or N, the heteroatoms on the side chain can optionally be protected with an O-, S- or N-protecting group.

Such protecting groups are well known in the art. N-protecting groups may be e.g. as disclosed above. O-protecting groups are e.g. described in "The Peptides", 3, 169-201. For aliphatic hydroxy functionalities, suitable O-protecting groups include the benzyl, t-butyl and methyl groups. For aromatic hydroxy functionalities, suitable O-protecting groups include the benzyl, t-butyl, methyl, tosyl and benzyloxycarbonyl groups. O-protecting groups for carboxy functionalities on amino acid side chains are well known ester groups, e.g. as described in "The Peptides", 3, 101-135, or amides and include the methyl, ethyl, t-butyl and benzyl groups or amide groups such as obtained with C₁₋₄alkyl-amine, C₁₋₄alkoxy-C₁₋₄alkyl-amine or aniline. S-protecting groups for thiol functionalities on amino acid side chains are known and described e.g. in "The Peptides", 3, 137-167. Examples include the methyl, t-butyl, benzyl, p-methoxyphenylmethyl, ethylamino-carbonyl and benzyloxycarbonyl groups.

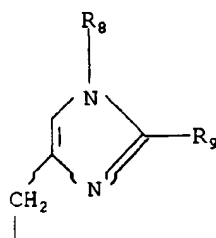
When A₁ is an amino acid residue having an optionally protected side chain, it may be an α-amino acid, e.g. Val, Leu, Ser, Ile, Gly, Ala, Phe, Pro or hydroxy-Pro, preferably Val, Leu, Ile or Ala.

When A₁ or A₂ is an α-hydroxy acid, it may be e.g. lactic acid or 2-hydroxy-3-methyl butanoic acid. Preferably only one of A₁ and A₂ is an α-hydroxy acid.

Examples of R₃ as an optionally protected side chain residue of an α-amino acid include a side chain residue as present in a natural α-amino acid and optionally protected, e.g. as present in Val, Leu, Ile, Ala, Thr, Ser, Cys, Met, Lys, Gly or Tyr or a radical of formula (d), (e) or (f)

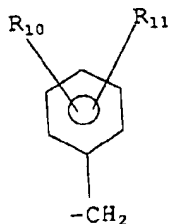


(d)



(e)

wherein each of R₈ and R₉, independently is H, halogen, C₁₋₄alkyl, CF₃ or trityl, and or



(f)

each of R₁₀ and R₁₁ independently is H, halogen, C₁₋₄alkyl, C₁₋₄alkoxy, CF₃, OH or phenyl.

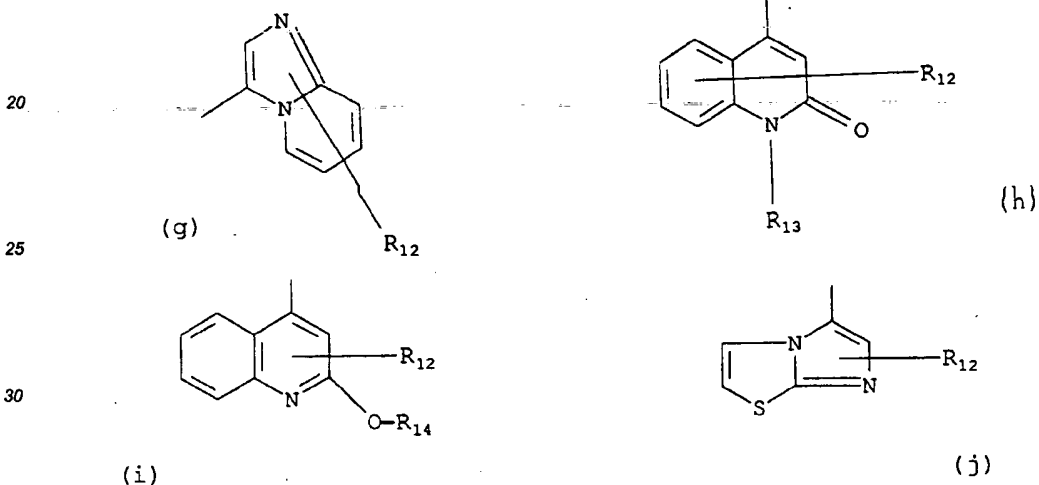
Examples of Y_5 as an optionally protected side chain residue of an α -amino acid include side chain residue as present in a natural α -amino acid, e.g. Val, Leu, Ile, Ala, Thr, Ser or Lys, preferably Val, Leu, Ile or Ala, and optionally protected.

Further examples of R_3 include optionally protected benzimidazol-2-yl-methyl, 1H-1,2,4-triazol-3-yl-methyl, pyrazol-3-yl-methyl or indazol-3-yl-methyl.

By cycloaliphatic residue as Y_1 , Y_2 , Y_3 or Y_6 is meant a polycyclic cycloalkyl radical joined to the CO by a tertiary carbon atom, e.g. adamantyl.

Examples of mono-, bi- or tricyclic heteroaryl as Y_1 or Y_6 are 5- or 6-membered aromatic heterocyclic residues, optionally condensed and optionally substituted, comprising at least one heteroatom selected from N, S or O. Such heterocyclic residues may also be condensed to 1 or 2 benzene rings and/or to a further heterocyclic ring. Preferably the heteroaryl residue comprises 1, 2 or 3 heteroatoms selected from N and S. Suitable examples include optionally substituted pyridyl, indolyl, indazolyl, acridinyl, xanthenyl, pyrrolyl, benzothienyl, a 5-membered unsaturated nitrogen-containing heterocyclic radical e.g. as disclosed below or a radical of formula (g), (h), (i), (j)

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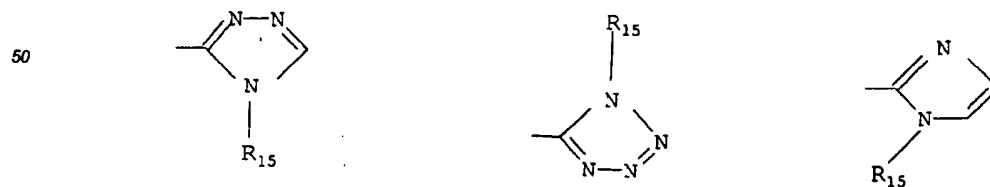
wherein R_{12} is H, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 , halogen, nitro, or cyano, and each of R_{13} and R_{14} independently is H or C_{1-4} alkyl.

Pyridyl as Y_1 , Y_2 , Y_3 or Y_6 is preferably a residue attached by a carbon atom to CO or X_1 and optionally substituted by 1, 2 or 3 substituents selected from halogen, CF_3 , nitro, cyano, C_{1-4} alkyl and C_{1-4} alkoxy.

Optionally substituted indolyl, indazolyl, acridinyl, xanthenyl, pyrrolyl or benzothienyl is preferably optionally protected or optionally C_{1-4} alkyl substituted 2- or 3-indolyl, 3-indazolyl, 9-acridinyl, 9-xanthenyl, 2-pyrrolyl, 2- or 3-benzothienyl.

Examples of bi- or tricyclic heteroaryl as Y_2 or Y_3 are optionally substituted bi- or tricyclic residues comprising at least one heteroatom selected from N, S or O and at least one unsaturated cyclic moiety, e.g. as indicated above for Y_1 or Y_6 .

5-membered nitrogen-containing heterocyclic radical as Y_3 may comprise 2, 3 or 4 nitrogen atoms; it may be unsaturated and also optionally substituted. Suitable examples include e.g.



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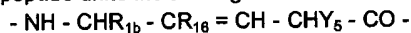
wherein R_{15} is H or C_{1-4} alkyl.

The term "pseudo-dipeptide" as used herein refers to a dipeptide isostere in which the peptide bond be-

tween the two amino acid residues, whether natural or unnatural, is replaced with an isosteric group, e.g. $C(Halogen)=CH-$.

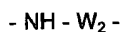
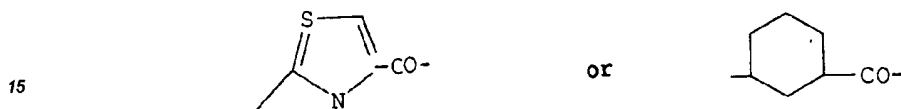
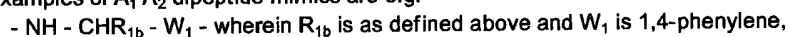
The term "dipeptide mimetics" as used herein means a chemical entity able to substitute a dipeptide in its biological properties. A "dipeptide mimetic" can have variable degrees of structural similarity with the dipeptide, mimicking e.g. only the dipeptide backbone or only the side chains of the dipeptide.

Examples of $A_1 A_2$ pseudo-dipeptide units include e.g.

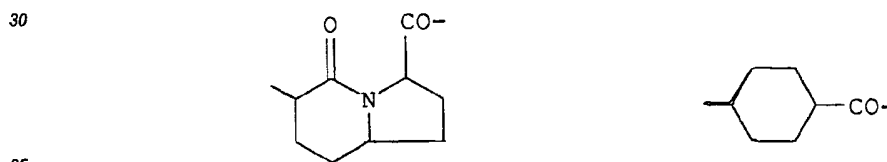
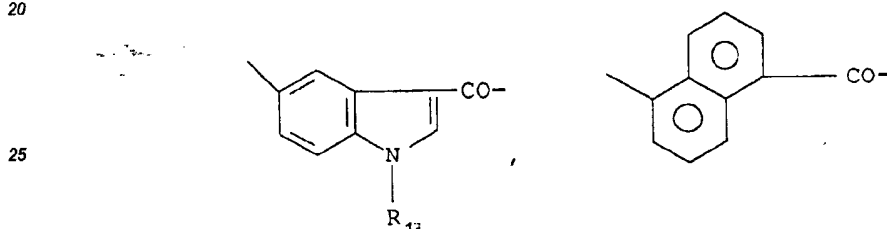


wherein R_{1b} and Y_5 are as defined above and R_{1a} is halogen or C_{1-4} alkyl.

Examples of $A_1 A_2$ dipeptide mimics are e.g.



wherein W_2 is



or



wherein R_{17} is H or C_{1-4} alkyl,
or $-O-W_3-$ wherein W_3 is



Aryl as Y_1 , Y_3 or Y_6 means phenyl, 1- or 2-naphthyl or 9-anthracyl. Preferably 9-anthracyl is unsubstituted. Substituted phenyl as Y_1 , Y_3 or Y_6 is phenyl bearing 1 to 5 fluoro substituents or phenyl mono-, di- or trisub-

stituted by substituents selected from hydroxy, C₁₋₄ alkyl, C₁₋₄alkoxy, nitro, halogen, acetyl, benzoyl, amino, NHCH₃, N(C₁₋₂alkyl)₂ cyano, CF₃, COOH, CONH₂, C₁₋₄alkoxycarbonyl, NHCOC₁₋₄alkyl, CONHSO₂-phenyl and -C₆(CH₃)₄-COOH. When Y₁, Y₃ or Y₆ is naphthyl, it may be unsubstituted naphthyl or 1-naphthyl substituted in position 2 by C₁₋₄alkyl, C₁₋₄alkoxy or CF₃.

5 Halogen means fluorine or chlorine.

By bioisosteric group as R₇ is meant a group replacing one part of a biologically active molecule without altering its essential biological features. Suitable examples of a bioisosteric group for carboxy include e.g. a tetrazolyl group.

10 Radical of formula (a) comprises one asymmetric carbon and radical of formula (b) comprises two asymmetric carbons. Accordingly these radicals lead to optical isomerism. It will be understood that the present invention includes all individual isomeric forms and diastereoisomers as well as mixtures, e.g. racemates unless otherwise stated.

By the term "physiologically-hydrolysable and -acceptable esters or amides" are meant esters and amides which are hydrolysable under physiological conditions to yield alcohols or amines which are themselves physiologically acceptable, i.e. which are non-toxic at the desired dosage levels.

15 Such esters or amides are obtained by esterification or amidation, respectively, of a compound of formula I wherein R₇ is a carboxy group. Such esters include esters with an aliphatic or alicyclic alcohol or polyol having 1 to 12 carbon atoms. Such amides include amides with aliphatic amines, e.g. C₁₋₄alkyl amine, C₁₋₄alkoxy-C₁₋₄alkyl amine such as β-methoxy-ethyl amine, or aniline.

20 The compounds of formula I may exist e.g. in free form, acid addition salt form or in the form of complexes thereof. Acid addition salts may be formed with e.g. organic acids, polymeric acids and inorganic acids. Such acid addition salt forms include e.g. the hydrochlorides and acetates. Salt forms may also include those obtainable with the carboxylic group present in compounds of formula I, e.g. alkali metal salts such as sodium or potassium, or substituted or unsubstituted ammonium salts. Complexes are e.g. formed from compounds of
25 formula I on addition of inorganic substances, e.g. inorganic salts or hydroxides such as Ca- and Zn-salts, and/or an addition of polymeric organic substances.

All α-amino acid residues present may have the D or L configuration, except otherwise stated, e.g. as in proviso (ii).

30 In the compounds of formula I, the following significances are preferred either individually or in any combination or sub-combination:

1. R is an amino protecting group or benzyloxy, preferably an amino protecting group e.g. benzyloxycarbonyl, naphthoyl naphthylsulfonyl optionally ring-substituted by di(C₁₋₄alkyl)-amino. R is preferably benzyloxy when A₁ is a radical of formula (α).

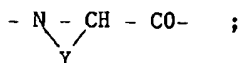
35 2. A₁ is Val, D-Val, Phe, Leu, Ala, Ile, trimethylsilyl-Ala or an α-hydroxy acid residue.

3. X is a radical of formula (a).

4. Monocyclic heteroaryl is optionally substituted pyridyl or 5-membered unsaturated nitrogen-containing heterocyclic radical.

5. A₂ is

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45 A₃ is -CH₂-X₁-CO-Y₁, -CH₂-O-Y₂ or -CH₂-S-Y₃.

6. A₁ is an α-hydroxy acid residue; A₂ is -NH-CHR₃-CO-; A₃ is -CH₂-X₁-CO-Y₁, -CH₂-O-Y₂ or -CH₂-S-Y₃.

7. Y₁ is substituted aryl, optionally substituted heteroaryl or a cycloaliphatic residue.

8. A₂ is -NH-CHR₃-CO-; A₃ is -CH₂-X₁-CO-Y₁ wherein Y₁ is a cycloaliphatic residue or optionally substituted bi- or tricyclic heteroaryl, or -CH₂-S-Y₃ wherein Y₃ is a cycloaliphatic residue or a 5-membered nitrogen-containing heterocyclic radical.

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9. A₂ is an α-hydroxy acid residue; A₃ is -CH₂-X₁-CO-Y₁, -CH₂-O-Y₂ or -CH₂-S-Y₃. Y₁, Y₂ or Y₃ is more preferably a cycloaliphatic residue or optionally substituted aryl or pyridyl.

10. In radical (c) R₄ is H.

11. R₆ is CO.

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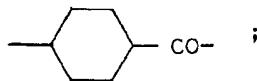
12. A₁ and A₂ form together a radical of formula (aa) wherein R_{1a} and R₆ form together a C₂₋₆alkylene, -CHY₅-CO- has the D configuration and A₃ is -CH₂-X₁-(CO)_m-Y₆ wherein Y₆ is optionally substituted aryl or pyridyl.

13. A₁ and A₂ form together a radical of formula (aa) wherein R_{1a} and R₆ form together a C₂₋₆alkylene, and A₃ is -CH₂-X₁-(CO)_m-Y₆ wherein Y₆ is other than optionally substituted aryl or pyridyl.

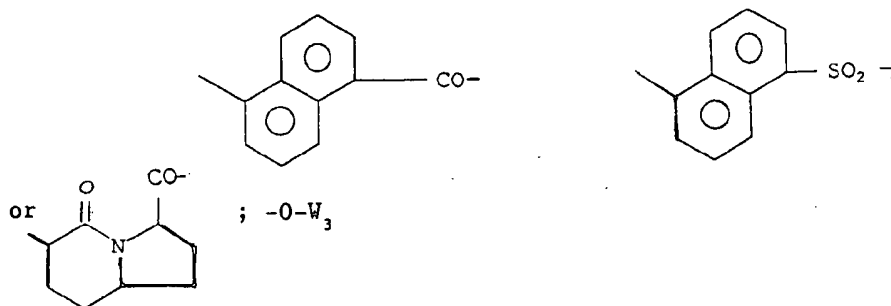
14. A_1 and A_2 form together a pseudo-dipeptide residue.

15. A_1 and A_2 form together a dipeptide mimetics residue; Y_6 is optionally substituted aryl or optionally substituted mono-, di- or tricyclic heteroaryl.

16. Preferred dipeptide mimetics residues are $-\text{NH}-\text{CHR}_{1b}-\text{W}_1-$ wherein W_1 is



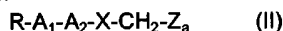
$-\text{NH}-\text{W}_2$ wherein W_2 is



17. R_7 is $-\text{CO}_2\text{H}$ or an ester thereof, preferably $-\text{CO}_2\text{H}$ or $(\text{C}_{1-12}\text{alkoxy})\text{carbonyl}$.

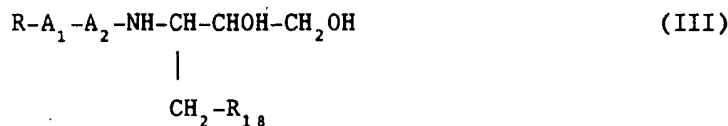
The present invention also provides a process for the production of a compound of formula I, which process comprises:

- removing at least one protecting group from a compound of formula I in protected form or adding a protecting group R at the terminal group of a compound of formula I; or
- converting one compound of formula I into another compound of formula I; or
- coupling together by an amide bond two peptide fragments, each of which contains at least one amino acid in protected or unprotected form and one peptide fragment containing a radical of formula (a) or (b) as defined above, the peptide fragments being such that a protected or unprotected peptide having the sequence according to formula I above is obtained and, if necessary, removing the protecting group or groups from a compound of formula I in protected form; or
- reacting a compound of formula II



wherein R, A_1 , A_2 and X are as defined above, and Z_a is a leaving group, with a compound of formula $\text{HX}_1(\text{CO})_m-\text{Y}_7$ wherein X_1 and m are as defined above and Y_7 is Y_1 , Y_2 , Y_3 or Y_6 or a functional derivative thereof when m is 1;

e) for the production of a compound of formula I wherein X is a radical of formula (a) or (b) monoalkylating or monoacylating a compound of formula III



wherein R, A_1 and A_2 are as defined above and R_{18} is an ester group, with a compound $\text{HX}_1-(\text{CO})_m-\text{Y}_7$ wherein m, X_1 and Y_7 are as defined above, or a functional derivative thereof, when m is 1.

and recovering a compound of formula I thus obtained in free or salt form or in the form of a complex.

Processes (a) to (e) above may be carried out in accordance with standard techniques known in the art.

The removal of a protecting group in process step (a) may also include the removal of R on the terminal group of a compound of formula I. For example, when R is benzyloxy carbonyl, this group may be removed by hydrogenation in the presence of a catalyst, e.g. Pd.

In accordance with process step (b) for example, for the production of a compound of formula I wherein X comprises a carboxy group, a compound of formula I wherein X comprises an esterified or amidated carboxy

group may be hydrolysed. Such hydrolysis may be effected by treatment with an appropriate alkali or by acid hydrolysis, for example in the presence of trifluoroacetic acid.

Furthermore, in accordance with process step (b), for the production of a compound of formula I wherein X comprises an esterified or amidated carboxy group, a compound of formula I wherein X comprises a carboxy group or an esterified carboxy group may be (trans) esterified or amidated. Such ester formation or amidation may be carried out using any of the techniques known in the art, for example converting the carboxy group in a functional reactive group, e.g. a corresponding acid halide or anhydride.

In accordance with a further embodiment of process step (b), for the production of a compound of formula I wherein X is a radical of formula (a), a compound of formula I wherein X is a radical of formula (b) may be oxidized. This process may be carried out in analogy to the known techniques used for the oxidation of an alcohol, e.g. according to Jones, Swern or Pfitzner-Moffatt oxidation procedures.

Process step (c) may be carried out by the techniques known in the art of peptide chemistry.

Functional derivatives of $HX_1-(CO)_m-Y_6$ when m is 1 include e.g. acid halides, for example acid chloride, anhydride, etc. Z_a may be e.g. halogen.

Process step (e) may also be carried out according to an esterification procedure, e.g. according to the Mitsunobu procedure.

Where desired, in these reactions, protecting groups may be used for functional groups which do not participate in the reaction. These may be e.g. amino protecting groups, carboxy protecting groups, acetal groups etc. When the desired reaction is complete, the protecting groups may then be removed.

Each of the above processes may be carried out using starting materials in the form of one or other of the individual optical isomers or in the form of mixtures [relating to the asymmetric carbons present in radicals of formula (a) or (b) as X or in such a radical precursor]. Conveniently the starting materials are used as S- or R-enantiomers to produce a compound of formula I wherein the asymmetric carbon in radicals of formulae (a) or (b) has the S or R configuration, respectively.

The starting materials used in process steps (d) or (e) may be prepared in analogy with process step (c). Insofar as the production of the starting materials is not particularly described, the compounds are known or may be prepared analogously to methods known and practiced in the art.

The following examples are illustrative of the invention. All temperatures are in °C.







The following abbreviations are used:

THF	= tetrahydrofuran
TFA	= trifluoroacetic acid
MeOH	= methanol
EtOAc	= ethyl acetate
DCC	= dicyclohexylcarbodiimide
HOBT	= hydroxybenzotriazole
Z	= benzyloxycarbonyl
Pip	= piperidine
BOC	= t-butoxycarbonyl
Fmoc	= 9-fluorenylmethoxycarbonyl
EDCI	= N-ethyl-N'-dimethylaminopropyl-carbodiimide hydrochloride
DMAP	= 4-dimethylaminopyridine
DAST	= diethylamino sulphur trifluoride
t.Bu	= tert.-butyl

EXAMPLE 1:

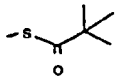

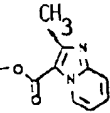
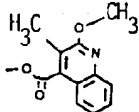
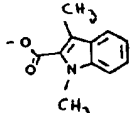
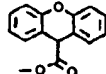
(3R)-3-[3-(3-benzyloxybenzoyl)aminobenzoyl]-amino-(4S)-4-hydroxy-5(1-adamantoyloxy)pentanoic acid ethyl ester

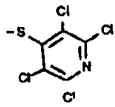
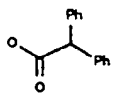
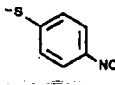
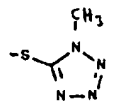
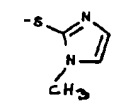
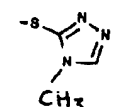
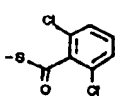
3-(3-benzyloxybenzoyl)aminobenzoic acid (0.44 g, 1.2 mmol) is dissolved in DMF (15 ml), HOBT.H₂O (0.2 g, 1.2 mmol) and DCC (0.53 g, 2.55 mmol) added, followed by (3R)-amino-(4S)-4-hydroxy-5(1-adamantoyloxy)pentanoic acid ethyl ester (0.4 g, 1.2 mmol) in DMF (4 ml). The reaction mixture is stirred over night, filtered and DMF evaporated. The residue is dissolved in EtOAc, adjusted to alkaline pH by adding NH₄OH conc. and chromatographed (SiO₂, acetone/hexane 15/85), yielding the title compound as a colorless foam.


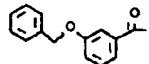
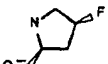
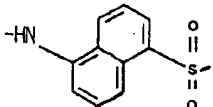
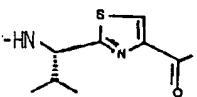
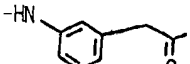
5	Ex.	R	A ₃	A ₄	Ry	Za	Characterization
10	5	Z	Val	Ala	Et		3R(1) 642(2)
	6	Z	Val	Ala	H	id.	3R 614
	7	Z	Val	Ala	t.Bu	id.	3R 670
15	8	Z	Val	Ala	Et	id.	3R,S(1) 642
20	9	Z	Val		Et	id.	3R 680
	10	Z	Val		Et	id.	3R 680
25	11	Z	Val	Ala	H		657
30	12	Z	Val	Ala	t.Bu	id.	713
35	13	Z	Val	Ala	H		595
	14	Z	Val	Ala	t.Bu	id.	651
40	15	Z	Val	Ala	H		552
	16	Z	Val	Ala	t.Bu	id.	608
45	17	Z	Val	Ala	Et	id. 3R	580

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Ex.	R	A ₃	A ₄	R _y	Z _A	Characterization
18	Z	Val	D-Ala	Et		3R 580
19	Z	Val	Ala	H	S-CS-N(Et) ₂	583
20	Z	Val	Ala	t.Bu	id.	639
21	Z	Val	Ala	Et		3R 591
22	Z	Val	Ala	H		610
23	Z	Val	Ala	t.Bu	id.	666
24	Z	Val	Ala	H		651
25	Z	Val	Ala	Et	id.	679
26	Z	Val	Ala	H		623
27	Z	Val	Ala	t.Bu	id.	679
28	Z	Val	Ala	Et	id.	651
29	Z	Val	Ala	H		660

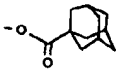



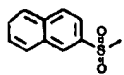
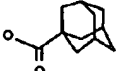
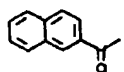
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10	30	Z	Val	Ala	H		683
15	31	Z	Val	Ala	H		646
20	32	Z	Val	Ala	H		589
25	33	Z	Val	Ala	t.Bu	id.	645
30	34	Z	Val	Ala	H		550
35	35	Z	Val	Ala	H		549
40	36	Z	Val	Ala	t.Bu	id.	605
45	37	Z	Val	Ala	H		548
50	38	Z	Val	Ala	t.Bu	id.	604
55	39	Z	Val	Ala	Et	 3R	669

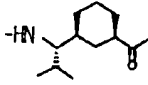

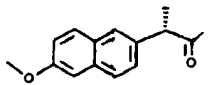
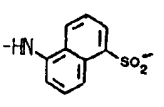
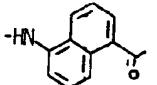
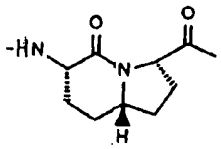
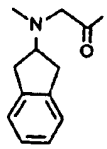
Ex.	R	A ₃	A ₄	R _y	Z _a	Characterization	
40	Z	Val	Lys (N ^ε -acetyl N ^ε -cyclohexyl)	Et		834	
41				t.Bu	id.	3S	702
42	id.	id.	id.	H	id.	3S	646
43	Z			H	id.	3S	660
44	Z	id.	id.	t.Bu	id.	3S	716
45	Z	id.	id.	Et	id.	3S	688
46	Z			Et	id.	3R	665
47	Z	id.	id.	H	id.	3R,S	637
48	Z			Et	id.	3R	3.3°(3)

5	Ex.	R	A ₃	A ₄	R _y	Z _a	Characterization
10	49	Z			Et		3R 4.6°(3)
	50	Z	id.	id.	H	id.	3S -0.5°(3)
15	51	Z	id.	id.	t.Bu	id.	3R -0.5°(3)
	52	Z	id.	id.	H	id.	3R -0.2°(3)
20	53	Z			Et	id.	3R 6.0°(3)
25	54	Z	id.	id.	H	id.	3R 601.5
	55	Z	id.	id.	t.Bu	id.	3R 0.2°(3)
30	56	Z			H	id.	3S 613
	57	Z	id.		Et	id.	3R 641
35	58	Z		Ala	H	id.	3R,S -23°(3)
40	59	Z	id.	Ala	Et	id.	3R 16.6°(3)
	60	Z	id.	Ala	t.Bu	id.	3R,S
45	61	Z	Val		H	id.	3R,S -11.1°(3)
	62	Z	Val	id.	t.Bu	id.	3R,S -6.9°(3)
	63	Z	Val	id.	Et	id.	3R 23.4°(3)

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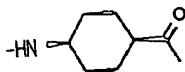

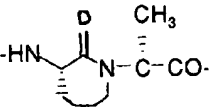
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Ex.	R	A ₃	A ₄	R _y	Z _n	Characterization
64	Z	Val	id.	Et		3R 19.9°(3)
65	Z	Ala	Pro	H		623
66	Z	Ala	Pro	t.Bu	id.	679
67	Z	Val		H	id.	665
68	Z	Val	id.	t.Bu	id.	721
69	Z	Val		H	id.	665
70	Z	Val	id.	t.Bu	id.	721
71	Z	Val	Spinacin	H	id.	703
72	Z	Val	id.	t.Bu	id.	759
73	Z	Val	Pro	H	id.	651
74	Z	Val	Pro	Et	id.	679
75	Z	Val	Pro	Et	id.	3R 679
76		Val	Ala	Et		3R 698
77		Val	Ala	Et	id.	3R 662

5	Ex.	R	A ₃	A ₄	R _y	Z _a	Characterization
10	78	Z			Et		664
15	79	Z			Et	id. 3R	53.4°(4)
	80	Z	id.	id.	Et	id. 3S	-30°(4)
	81	Z	id.	id.	H	id. 3R	44.4°(4)
20	82	Z	id.	id.	H	id. 3S	-19.5°(4)
25	83	Z			H	id. 3S	660
	84	Z	id.	id.	t.Bu	id. 3S	716
	85	Z	id.	id.	Et	id. 3R	688
30	86	Z			H	id. 3R,S	624
35	87	Z			H	id. 3S	635
40	88	Z	Val 		H	id. 3R,S	727
45	89	Z	Val	id.	t.Bu	id. 3R,S	783

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Ex.	R	A ₃	A ₄	R _y	Z _a	Characterization
90	Z			H		3R,S 580
91	Z	id.	id.	t.Bu	id.	3R,S 636
92	Z			H	id.	3S 637
93	Z	id.	id.	t.Bu	id.	3S 697
94	Z	id.	id.	Et	id.	3S 665
95	Z	$\text{-NH-CH-CCl=CCH}_3\text{-CO-}$ $\text{CH(CH}_3)_2$		H	id.	6°(4)
96	Z	$\text{-NH-CH-CCl=C(CH}_3\text{)-CO-}$ $\text{CH(CH}_3)_2$		H	id.	-21°(4)

(1): configuration
 (2): MH⁺ (MS m/z)
 (3): [α]_D²⁰ in CHCl₃
 (4): [α]_D²⁰ in methanol

Z protected 2-(1-(S)-aminoisobutyl)thiazole-4-carboxylic acid is used in the preparation of compound of Example 46 and is prepared according to the method described by T.Shiori et al. in J.Org.Chem. 1987, 52, 1252 from Z-valinal and cysteine methyl ester.

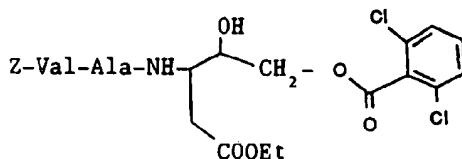
Z protected racemic cis-3-(1-aminoisobutyl)cyclohexane-1-carboxylic acid is used in the preparation of compound of Example 78 and is prepared as a racemate by a multiple synthesis: 3-oxabicyclo[3.3.1]nonane-2,4-dione (T. Yamazaki et al. Chem. Pharm. Bull. 1987, 35(8), 3453) is reacted with Li-salt of isobutyric acid t.-butyl ester. The resulting acid is converted into its methyl ester, the t.butyl ester deesterified with TFA and decarboxylated at 145° to provide cis-3-(1-oxo-2-methylpropyl)-1-cyclohexane carboxylic acid methyl ester. The latter keto-ester is converted into its oxime and hydrogenated over PtO₂ in acetic acid to the corresponding amino ester which is cyclized upon heating to 50° to give two lactams (2:1) separated by fractional crystallization. The major component (3-azabicyclo[3.3.1]nonan-3-(endo)isopropyl-1-one: m.p.133-134.5°, crystallized from ether/hexane) is hydrolyzed to the corresponding amino acid by refluxing in 35% HCl for four days and protected with Z.

Z protected (3S,6S,S9)-6-amino-5-oxo-indolizidin-3-carboxylic is used in Example 87 and is prepared by reacting 2,2-bis(2-iodoethyl)-1,3-dioxolane with 2 equivalents of (2R)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopro-

pylpyrazine according to the "bislactim ether method" developed by Schoellkopf (U. Schoellkopf, Pure & Appl. Chem. 1983,55,1799) to yield after hydrolysis of the intermediate ketone and reductive amination (Pd/C, ethanol, 1 atm H₂) followed by spontaneous cyclization the desired indolizidine derivative. The free amino group is Z-protected and the ester hydrolyzed to give the desired indolizidine derivative.

Z-protected (2R,3Z,5S)-5-amino-4-chloro-2,6-dimethyl-3-heptenoic acid used in the preparation of compound of example 96 may be prepared as follows: the allylic alcohol resulting of a syn-aldol-condensation of N-propionyl-10,2-sultam with the (E/Z)-2-chloro-4-methyl-2-pentenal as described by W. Oppolzer [JACS 112, 2767 (1990)] is thermally rearranged as its trichloroacetimidate [L.E. Overman, JACS, 98, 2901 (1976)]. This intermediate is hydrolyzed to the free amino acid and then protected.

EXAMPLE 97:



MH⁺: 644

The compounds of formula I, their physiologically-hydrolysable and -acceptable esters and amides and their pharmaceutically acceptable salts (hereinafter referred to as compounds of the invention) exhibit pharmaceutical activity and are, therefore, useful as pharmaceuticals.

In particular, the compounds of the invention inhibit IL-1 β secretion as indicated in the following in vitro test using THP-1 cells and in vivo test methods:

a) 900 μ l THP-1 cells (0.5 x 10⁶ cells) together with 100 U γ -interferon/0.9 ml RPMI 1640 medium (containing 2 mM L-glutamine and 5 % heat-inactivated foetal calf serum) are pipetted into 24 well culture plates. 100 μ l of the compound to be tested are then added. After 3 hours at 37 ° C in 5 % CO₂/95 % air, 10 μ l lipopolysaccharide 500 μ g/ml is added and the incubation continued for a further 40 hours. Appropriate controls (with and without stimulus, solvent) are also included. The media are then removed and clarified by centrifugation at 1000 g for 10 min. 1.0 ml digitonin 0.01 % is added to the wells to lyse the cells which are loosened by scraping with a rubber policeman and left at 4 ° C for 10 min. Lactate dehydrogenase measurements are then performed immediately and the samples stored at - 20 ° C until the other determinations can be made. The assays are: IL-1 β (medium and lysate), IL-6 (medium), TNF- α (medium), PGE₂ (medium and lysate), lactate dehydrogenase (LDH) and DNA (lysates). IL-1 β , IL-6 and TNF- α assays are determined using commercially available ELISA kits (Cistron), PGE₂ is measured using a standard RIA and DNA fluorimetrically using DAPI.

In this test, the compounds of the invention selectively inhibit IL-1 β release in concentrations from about 0.01 to 100 μ M. In contrast IL-6, TNF- α , PGE₂ and DNA levels remain substantially unaffected, and the compounds are non-toxic, since LDH release is unchanged.

b) LPS-Fever

A LPS-suspension (Sigma, No. L-5886; 100 μ g/5ml glucose solution/kg s.c.) is injected in male Türlingen SD rats (150-160g). 2 hours later the body temperature is measured using a thermistor rectal probe connected to an ELLAB telethermometer. After 4 hours the test compound is administered p.o. 2 hours later (6 hrs after LPS administration) the temperature is measured again. The temperature increment shown by the untreated controls is taken as 100% and that in the treated group is expressed as a percentage of this value. The ED₅₀ is the dose causing a 50% inhibition of the temperature increase determined in the control rats. In this test compounds of the invention inhibit the LPS-induced temperature increase when administered at a dosage in the range of from 0.001 to 0.1 mg/kg p.o.

Compounds of the invention are therefore indicated for use in the treatment of disorders with an aetiology associated with or comprising excessive IL-1 β release, e.g. in a wide variety of inflammatory states and diseases, for example tissue calcium depletion, degenerative processes in bone and cartilage, e.g. rheumatoid arthritis and osteoarthritis, inflammatory bowel disease, irritable bowel disease, septic shock, psoriasis, asthma, adult respiratory distress syndrome, diabetes type I, allergic skin disorders, osteoporosis of various genesis including e.g. climacteric or post-menopausal osteoporosis as well as osteoporosis consequential to old age, immobilization or trauma, arteriosclerosis, Alzheimer disease, acute or chronic myelogenous leukemia or a variety of autoimmune disease states.

For the above indications the required dosage will of course vary depending upon, for example, the com-

pound of the invention employed, the mode of administration, the particular condition to be treated and the effect desired. An indicated daily dosage is of the order of from about 0.1 mg to about 1 g/day, conveniently administered once, in divided dosages 2 to 4 x/day, or in sustained release form.

In accordance with the foregoing the present invention also provides:

a) A compound of formula I, a physiologically-hydrolysable and -acceptable ester or amide thereof or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical, for example in the treatment of above indicated disorders, e.g. for use as an anti-inflammatory agent.

The compounds of the invention may be administered by any conventional route, in particular nasally, enterally, e.g. orally, e.g. in the form of tablets or capsules, or parenterally e.g. in the form of injectable solutions or suspensions or in a suppository form. Unit dosage forms contain, for example from about 25 µg to 500 mg of a compound of the invention.

The compounds of the invention may be administered in free form or in pharmaceutically acceptable salt form. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

Furthermore the present invention also provides:

b) A pharmaceutical composition comprising a compound of formula I, a physiologically-hydrolysable and -acceptable ester or amide thereof or a pharmaceutically acceptable salt thereof, as hereinbefore defined, together with a pharmaceutically acceptable diluent or carrier therefor. Such compositions may be manufactured in conventional manner.

Compounds of the invention have an interesting pharmacological profile in view of their in vitro and in vivo activity. Compounds of formula I wherein A_2 is optionally substituted proline, or A_1 and A_2 form together a radical of formula (aa) or a dipeptide mimetics residue are particularly preferred.

Claims

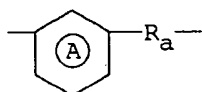
1. A compound of formula I



wherein

R is hydrogen, an amino or hydroxy protecting group or optionally ring substituted benzyloxy,

A_1 is an α -hydroxy acid residue; an amino acid residue or a thiocarbonyl analogue thereof having each an optionally protected side chain; or a radical of formula (α)

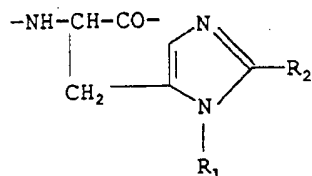


(α)

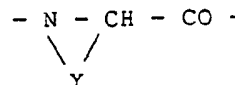
wherein ring A is optionally substituted by hydroxy or C_{1-4} alkoxy and R_a is CO or CS

and either

i) A_2 is an α -hydroxy acid residue, $-NH-CH(R_3)-CO-$



or



wherein

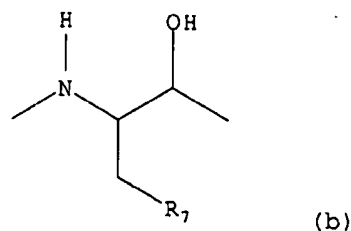
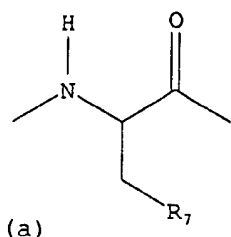
R_1 is C_{1-4} alkyl

R_2 is H, halogen, C_{1-4} alkyl, CF_3 or trityl,

R_3 is an optionally protected side chain residue of an α -amino acid, and

Y is C_{2-5} alkylene optionally substituted by OH, CH_3 , C_2H_5 , oxo, ketal or halogen,

X is a radical of formula (a) or (b)



wherein R_7 is $-\text{CO}_2\text{H}$, $-\text{CONHOH}$ or a bioisosteric group,

A_3 is $-\text{CH}_2-\text{X}_1-\text{CO}-\text{Y}_1$; $-\text{CH}_2-\text{O}-\text{Y}_2$; or $-\text{CH}_2-\text{S}-\text{Y}_3$; wherein X_1 is O or S, Y_1 is a cycloaliphatic residue; optionally substituted aryl; optionally ring substituted diphenylmethyl; piperidino; or optionally substituted mono-, bi- or tricyclic heteroaryl; Y_2 is a cycloaliphatic residue; optionally ring substituted diphenylmethyl; or optionally substituted bi- or tricyclic heteroaryl; Y_2 being also optionally substituted pyridyl or aryl when A_1 is other than an α -hydroxy acid residue and A_2 is other than $-\text{NH}-\text{CHR}_3-\text{CO}-$; and Y_3 is a cycloaliphatic residue; tri- $(\text{C}_{1-4}\text{alkyl})$ methylcarbonyl, di- $(\text{C}_{1-4}\text{alkyl})$ aminothiocarbonyl, 4-nitro-phenyl, 2,6-dichloro-benzoyl; 2,3,6-trichloro-4-pyridyl, a 5-membered nitrogen-containing heterocyclic radical or optionally substituted bi- or tricyclic heteroaryl; Y_3 being also optionally substituted pyridyl or aryl when A_1 is other than an α -hydroxy acid residue and A_2 is other than $-\text{NH}-\text{CHR}_3-\text{CO}-$;

or

ii) A_2 is a radical of formula (c)



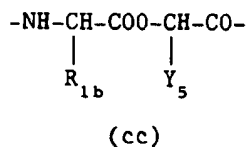
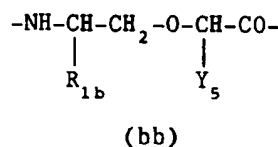
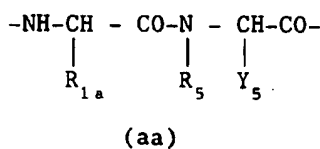
wherein

R_4 is H or $\text{C}_{1-4}\text{alkyl}$

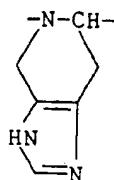
R_6 is CO or CS

Y_4 is $-(\text{CH}_2)_s-\text{N}(\text{C}_{1-4}\text{alkyl})_2$ or optionally protected $-(\text{CH}_2)_s-\text{NH-cyclohexyl}$ wherein s is 1, 2, 3 or 4;

or A_1 and A_2 form together a radical of formula (aa), (bb) or (cc)



wherein R_{1a} and R_5 form together $\text{C}_{2-5}\text{alkylene}$ or $\text{C}_{2-5}\text{alkenylene}$ and Y_5 is an optionally protected side chain residue of an α -amino acid; or Y_5 has one of the significances given above for Y_4 , or R_5 and Y_5 form together



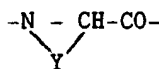
or R_5 is 2,3-dihydro-2-indanyl, Y_5 is H and R_{1a} has independently one of the significance given for R_{1b} , and R_{1b} is an optionally protected side chain of the amino acid residue or thiocarbonyl analogue A_1 indicated above, or A_1 and A_2 form together a pseudo-dipeptide or a dipeptide mimetics residue,

X is a radical of formula (a) or (b) as defined above, and

A_3 is $-\text{CH}_2-\text{X}_1-(\text{CO})_m-\text{Y}_6$ wherein X_1 is as defined above, m is 0 or 1 and Y_6 is a cycloaliphatic residue; tri- $(\text{C}_{1-4}\text{alkyl})$ methyl; optionally ring substituted diphenylmethyl; optionally substituted aryl; or an optionally substituted mono-, di- or tricyclic heteroaryl residue with the provisos that

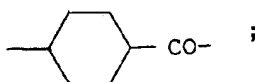
i) Y_1 in A_3 is other than optionally substituted aryl or pyridyl when A_1 is other than an α -hydroxy acid residue, A_2 is $-\text{NH}-\text{CHR}_3-\text{CO}-$ and R_7 in (a) or (b) is optionally esterified COOH ,
 ii) Y_5 in (aa) is in R configuration when it is the residue of an optionally protected side chain residue of an α -amino acid, Y_6 is optionally substituted aryl and R_7 is optionally esterified COOH , and the physiologically-hydrolysable and -acceptable esters or amides thereof when R_7 is $-\text{CO}_2\text{H}$, in free form, in salt form or in the form of complexes.

2. A compound according to Claim 1 wherein A_2 is

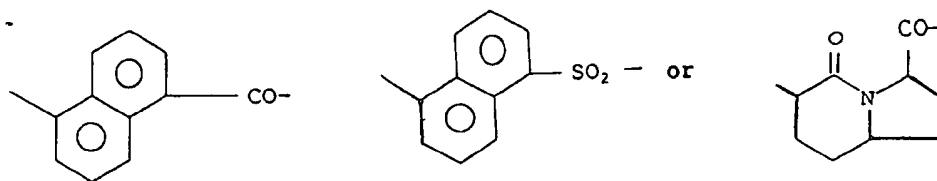


X is a radical of formula (a) as defined in Claim 1 and A_3 is $-\text{CH}_2-\text{X}_1-\text{CO}-\text{Y}_1$, $-\text{CH}_2-\text{O}-\text{Y}_2$ or $-\text{CH}_2-\text{S}-\text{Y}_3$ wherein Y , Y_1 , Y_2 , Y_3 and X_1 are as defined in Claim 1.

3. A compound according to Claim 1 wherein A_1 is an α -hydroxy acid residue, X is a radical of formula (a) as defined in Claim 1, A_2 is $-\text{NH}-\text{CHR}_3-\text{CO}-$ and A_3 is $-\text{CH}_2-\text{X}_1-\text{CO}-\text{Y}_1$, $-\text{CH}_2-\text{O}-\text{Y}_2$ or $-\text{CH}_2-\text{S}-\text{Y}_3$ wherein R_3 , X_1 , Y_1 and Y_2 are as defined in Claim 1 and Y_3 is a cycloaliphatic residue or a 5-membered nitrogen-containing heterocyclic radical.
4. A compound according to Claim 1 wherein A_1 is other than an α -hydroxy acid residue, A_2 is an α -hydroxy acid residue, X is a radical of formula (a) as defined in Claim 1 and A_3 is $-\text{CH}_2-\text{X}_1-\text{CO}-\text{Y}_1$, $-\text{CH}_2-\text{O}-\text{Y}_2$ or $-\text{CH}_2-\text{S}-\text{Y}_3$ wherein X_1 , Y_1 , Y_2 and Y_3 are as defined in Claim 1.
5. A compound according to Claim 1 wherein A_1 and A_2 form together a radical of formula (aa) wherein R_{1a} and R_5 form together $\text{C}_{2-6}\text{alkylene}$, $-\text{CHY}_5-\text{CO}-$ has the D configuration, X is a radical of formula (a) as defined in Claim 1 and A_3 is $-\text{CH}_2-\text{X}_1-(\text{CO})_m-\text{Y}_6$ wherein Y_6 is optionally substituted aryl or pyridyl.
6. A compound according to Claim 1 wherein A_1 and A_2 form together a dipeptide mimetics residue.
7. A compound according to Claim 1 wherein A_1 and A_2 form together a dipeptide mimetics residue of formula $-\text{NH}-\text{CHR}_{1b}-\text{W}_1-$ wherein R_{1b} is as defined in Claim 1 and W_1 is

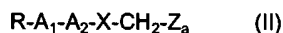


a residue of formula $-\text{NH}-\text{W}_2-$ wherein W_2 is



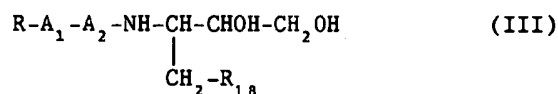
or a residue of formula $-O-W_3-$ as defined in Claim 1.

- 10 8. A process for the preparation of a compound of formula I as defined in Claim 1, which process comprises:
- a) removing at least one protecting group from a compound of formula I in protected form or adding a protecting group R at the terminal group of a compound of formula I; or
 - b) converting one compound of formula I into another compound of formula I; or
 - 15 c) coupling together by an amide bond two peptide fragments, each of which contains at least one amino acid in protected or unprotected form and one peptide fragment containing a radical of formula (a) or (b) as defined in Claim 1, the peptide fragments being such that a protected or unprotected peptide having the sequence according to formula I above is obtained and, if necessary, removing the protecting group or groups from a compound of formula I in protected form; or
 - 20 d) reacting a compound of formula II



wherein R, A_1 , A_2 and X are as defined in Claim 1, and Z_a is a leaving group, with a compound of formula $HX_1-(CO)_m-Y_7$ wherein X_1 and m are as defined in Claim 1 and Y_7 is Y_1 , Y_2 , Y_3 or Y_6 or a functional derivative thereof when m is 1;

25 e) for the production of a compound of formula I wherein X is a radical of formula (a) or (b) monoalkylating or monoacylating a compound of formula III



wherein R, A_1 and A_2 are as defined in Claim 1 and R_{18} is an ester group, with a compound $HX_1-(CO)_m-Y_7$ wherein m, X_1 and Y_7 are as defined above, or a functional derivative thereof when m is 1;

35 and recovering a compound of formula I thus obtained in free or salt form or in the form of a complex.

9. A compound of formula I according to any one of Claims 1 to 7, a physiologically-hydrolysable and -acceptable ester or amide thereof or a pharmaceutically acceptable salt thereof for use as a pharmaceutical.
- 40 10. A pharmaceutical composition comprising a compound of formula I according to any one of Claims 1 to 7, a physiologically-hydrolysable and -acceptable ester or amide thereof or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier therefor.
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